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10/562,345	02/07/2006	Dennis Heemskerk	4662-116	4007

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,345	HEEMSKERK ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/28/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims Construction

Claim 1 lists two intended results of the process, viz., yield, of at least 70%, and concentration of the hydrolysis product DH below 2%. These are not deemed to be actual claim limitations. It is only the actual steps which are claim limitations. Intended results do not limit the claims, but instead are just a statement of intention. There are no actual steps designed to achieve these results. The same applies to the "said reacting results in a conversion .... of at least 80%..." in claim 2.

In the specification, applicants state that it is concentration of the hydrolysis product DH below 2% which gives the result of yields of at least 70%. This statement is accepted at face value, but the claims contain no step designed to keep the concentration of DH below 2%. Claim 1 as written simply recites the two reactants and the enzyme.

In this regard, it is noted that the specification states that keeping concentration of the hydrolysis product DH below 2% the can be done by "by controlling the pH of the reaction mixture and/or the temperature." Similar language appears in e.g. claim 4. However, no such language actually appears in claim 1. Moreover, as noted in the indefinite rejection below, this language has no actual meaning. "Controlling" could mean setting minimum or a maximum or a range. It could mean limiting the speed at which the pH or temperature rises or falls. While the language of claim 4 is a claim limitation, because it constitutes an actual step, it does not as a practical matter limit the claim because it has no specific meaning. Indeed, the very next sentence in the specification says, "The pH and temperature applied may vary between wide ranges." Varying widely is the opposite of control.

The same is true for the claim 29 limitation. While formally this is a claim limitation, because it constitutes an actual step, it does not as a practical matter limit the claim because it has no specific meaning. That is, the specification does not say what the pH and temperature ranges are which accomplish this.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13, 16-18, 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/04086.

See example 4. This uses the dihydrophenylglycine in the form of the methyl ester, which is an activated form. Even if concentration of the hydrolysis product DH below 2% were a claim limitation, after 26 minutes, according to Table 4.1, the S/H is 12, which is actually higher than applicants report in example I. As noted in the IPER, taking into account the 40% conversion, that only amounts to about 0.15%, so that the reaction at that point would still anticipate. As for claim 22, the percentage will eventually fall to that point as the starting material is depleted.

Note that according to the specification, the goal of low DH percentage can be done by keeping pH in the 6-9 range. The pH as given is 7.5 and 7.0 in the two runs. The specification also says that it can be done by controlling the temperature from -5°C to 35°C. This was done at room temperature, generally taken as a little below 25°C. Therefore, while

the specification teaches that while setting either the pH or temperature in the proper range will do the job, this reference teaches doing both.

With regard to claim 22, the amount of 7-ADCA will eventually fall as the starting material is depleted.

With regard to claim 16, note that it is only "preferably according to claim 1", and thus does not require any concentration limitation.

Claims 1-10, 12-13, 16-22, 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by 4073687.

See example 7, which refers to example 1, which prepares a virtually identical cephalosporin. In example 1, 0.5 g of dihydrophenylglycine along with 0.1 g 7-ADCA. Example 7 repeats the 0.1 g 7-ADCA and says that it uses "similar"conditions, so it may be presumed that again, 0.5 grams of the acylating agent (dihydrophenylglycine in the form of the methyl ester) was employed. 100 g of water solvent are used, so that the concentration of dihydrophenylglycine is already below 0.5% even before the aqueous sodium carbonate is added. Indeed, this reaction appears to be run under substantially more dilute conditions than applicants use. Note that Aphanocladium aranearum is a source of penicillin acylase.

Even if the percentage of DH were a claim limitation, it is noted that at pH=6 and 30℃, both of the conditions which the specification teaches for achieving this have been done.

Note that in example 1, the product is recrystallized, and recovered as a hydrate, and presumably the same is done in example 7.

Claims 31-32 are rejected under 35 U.S.C. 102(b) as being anticipated by 5034522, 3819620, 3485819, 5278157, or 4139702.

The references provide synthesis of the hydrates. Claim 31 is in product by process form. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. See: ***In re Thorpe,*** 227 USPQ 964; ***In re Hirao,*** 190 USPQ 15 (see footnote 3); ***Ex parte Edwards,*** 231 USPQ 981; ***In re Pilkington***, 162 USPQ 145, 147; ***In re Dilnot,*** 133 USPQ 289, and MPEP 2113.

Claim 32 has a claim limitation on which the references are silent, the absorbance at 450 nm, presumably a type of purity limitation. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the absorbance at 450 nm. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the

function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the absorbance at 450 nm.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. In every reference applied, the reference explicitly teaches exactly what the compound is. In fact, it is the opposite. In a normal inherency situation, the claim is of known structure, and the reference is of unknown structure. Here, the reverse is true, and hence the legal circumstances of inherency-in-the-prior-art do not apply. The only difference is the property about which the reference happens to be silent. Recitation of a property, inherently possessed by the prior art thing, does not distinguish a claim drawn to those things from the prior art, ***In re Swinehart***, 169 USPQ 226, 229.

See for example ***Ex parte Anderson***, 21 USPQ 2d 1241 at 1251, discussion of Rejection E. The claims had "numerical or functional values for certain properties which [the authors of the references] did not measure". The PTO presented no reasoning as to why the prior art material would have been expected to have those properties. Instead, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253).

In another example, certain claims of ***Ex parte Raychem Corp.*** 25 USPQ2d 1265 required a linearity ratio of less than 1.2. The decision notes that neither reference discloses any values of the linearity ratio. The PTO presented no reasoning as to what the ratio would be expected to be in the references. The Decision states: "However, this does not end the

inquiry since, where the Patent and Trademark Office is not equipped to perform the needed testing, it is reasonable to shift the burden of proof to Raychem to establish that (1) the argued difference exists...."

And indeed, there have been a number of cases in which applicants have pointed to silence of the prior art with regard to this or that property: ***In re Pearson***, 181 USPQ 641; ***In re Zierden*** 162 USPQ 102; ***In re Lemin***, 140 USPQ 273; ***Titanium Metals Corporation of America v. Banner***, 227 USPQ 773; ***In re Benner,*** 82 USPQ 49; In re Wilder, 166 USPQ 545; ***Ex parte Kucera***, 165 USPQ 332; ***General Electric Co. v. Jewel Incandescent Lamp Co.***, 67 USPQ 155; ***In re May***, 574 F.2d 1082, 1090, 197 USPQ 601, 607; ***In re Parker***, 43 USPQ 457. Such efforts to avoid anticipation on that basis invariably failed. Going further, if silence about properties of prior art compounds could be relied on, then one could not reject over references with no utility (see I***n re Schoenwald***, 22 USPQ2d 1671), since applicants could always insert the utility into the claim as a property.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's burden under these circumstances was described in ***In re Best***, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 19-21, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/04086 or 4073687.

Although crystallizing the product is not mentioned, such would be obvious, since the commercial form of cephradine is crystalline. Removing the enzyme would be a necessity, and routine as the enzyme in WO 97/04086 is immobilized.

With regard to claim 20, this is a very light requirement. Equimolar amounts of the reactants are present. If more than half of the 7-ADCA is converted to cephradine, the ratio will rise above 0.7.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/04086 or 4073687 in view of WO 98/56944.

Claim 30 has the special feature of using sodium bisulfite. WO 98/56944 teaches specifically the advantage of using this generally (see abstract), giving material of better quality. The context is basically the same type of penicillin acylase.

Claims 1-17, 19-21, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/02663.

All aspects of the invention appear to be disclosed in the reference. Page 9, line 31 gives a preferred pH range of 6.1-7 and 20-30°C is at line 26. Enzyme separation appears at page 16, lines 14-16. Product crystallization is at page 10, line 20, with batch process at line 15, and at page 10, lines 14-18 and page 2 lines 15-23. The reactant 7-ACDA is at page 7 line 19 and esters of dihydrophenylglycine at lines 32-33, with the cephradine product named at page 8, line 22. The enzyme source appears at page 8-middle of page 9. High yields are a specific goal, with 85% in Example 1, and 88% in example 2. Although there is no working example to cephradine, it would be obvious to do so, as it is one of only 8 β-lactams listed in claim 9.

Claims 1-17, 19-21, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/31109.

Much the same is true for this reference as well. There are only two cephalosporins taught, cephradine and cefaclor. The actual working example happens to make cefaclor, but it would be obvious to do the same thing with cephradine since it is the only other one taught. Note that it is done at 10°C and pH=7.0. Yields were 84.6% and >90%. The

reference does employ naphthol additives, but the claims are open-ended ("comprising...") and hence are embracive of using such additives in the acylation process as seen in Example IV of the reference.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The claim 4 language is indefinite because this language has no actual meaning. "Controlling" could mean setting minimum or a maximum or a range. It could mean limiting the speed at which the pH or temperature rises or falls. While the language of claim 4 is a claim limitation, because it constitutes an actual step, it does not as a practical matter limit the claim because it has no specific meaning. Indeed, the very next sentence in the specification says, "The pH and temperature applied may vary between wide ranges." Varying widely is the opposite of control.

2. A similar problem occurs with claim 29. It is unduly functional, as it does not say what the pH and temperature is. pH and temperature can be precisely defined by numbers, and this must be done. See e.g. claims 8-9.
3. Claim 27 does not make sense. Where is this "dissolving" taking place? Dissolving in what? And dissolving will just give a solution? It is impossible to tell what the claim has in mind.
4. Further the reference to the hydrate being in the reaction mixture is unclear. The hydrate does not exist until the crystallization process.
5. The "concentration ... in the reaction mixture is below 2%" has two possible meanings. It could be met by being below 2% the entire time, or it could be met by being below 2% for just some part of the time.
6. A similar problem occurs with the S/H ratio. As the specification notes, this changes as the reaction proceeds.
7. The use of "preferably" is improper alternative language. It is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).
8. Claim 13 is unclear. The S/H does not depend just on the enzyme, but also on the conditions e.g. temperature and pH employed, concentration and relative amounts of the two reactants. Suppose that the enzyme was better under some conditions but not others?
9. Claim 18 is unclear. What does "mutant" mean? How can one be certain that a given enzyme is "mutant"?

10. The 0% in claim 22 makes no sense. If there is no 7-ADCA present, the reaction cannot take place.

Claims 19-21, 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As written, these are a process for crystallizing cephradine, but in fact, it is the monohydrate which is actually crystallized.

Claims 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim says "hydrate" but in fact, cephradine forms both a monohydrate and a dihydrate, but Example III here produced only the monohydrate. Applicants have not demonstrated that this process produces both hydrates, and it would be surprising if it did.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the even that applicants actually argue that the conversion and concentration of DH language really is a claim limitation, then the claims lack written description. The

claims would thus cover all methods of producing these results, not just the ones described in the specification. The specification teaches only "by controlling the pH of the reaction mixture and/or the temperature", not other methods, and applicants are thus not entitled to claim them.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

7/10/2008